REMARKS

Reconsideration and withdrawal of the rejections set forth in the Office action dated January 30, 2002 are respectfully requested. Applicants petition the Commissioner for a 3-month extension of time. A separate petition accompanies this amendment.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page(s) is/are captioned **"Version With Markings to Show Changes Made."**

I. Amendments

A. Specification

The specification has been amended for clarity. The specification has further been amended to amend the abstract along the lines of the Examiner's kind suggestion.

B. Claims

Claims 3 and 4 are re-written as independent claims.

Claims 2 and 5 are amended to depend from claim 3.

Claim 12 has been amended to correct a typographical error. Claim 12 has additionally been amended to depend from claims 3 and 4.

New claims 15 and 16 find support in original claims 2 and 5, respectively.

C. Drawings

Applicants proposed amendments to the drawings are indicated on the enclosed red-lined drawing sheet and are fully described above. Also enclosed is an amended drawing sheet.

By these amendments, no new subject matter has been added.

II. Information Disclosure Statement

The Examiner kindly pointed out that the references listed on page 2, lines 5-9 have not been considered. Applicants submit herewith a Supplemental Information Disclosure Statement in accord with 37 C.F.R. §1.98 listing all references cited on page 2 of the specification.

III. Objections to drawings under 37 C.F.R. §1.83(a)

The drawings were objected to under 37 C.F.R. §1.83(a) for allegedly failing to show every feature of the invention specified in the claims. Specifically, the Examiner alleges that Figure 1 fails to show a line defined by 1a-1a as described in the specification.

Applicants submit herewith a proposed amendment to Figure 1 showing a partial phantom line defined by 1a-1a..

Accordingly, Applicants respectfully request withdrawal of the objection under 37 C.F.R. §1.83(a).

III. Objections to Specification

The Examiner objected to the abstract because the sentence on page 11, lines 8-9 is allegedly ambiguous. Applicants have amended the abstract along the lines of the Examiner's kind suggestion.

The Examiner further objected to the disclosure for alleged informalities. The Examiner had 15 specific objections, which are set forth and addressed below.

1. Page 1, lines 21-22:

The Examiner alleges that the sentence is ambiguous. Applicants have amended the sentence for clarity.

2. Page 1, lines 27-29:

The Examiner objected to the term "adventitious" as allegedly rendering ambiguity in the process of pressurization. Applicants have amended the specification to clarify that the concern is "unintentional pressurization".

3. Page 1, lines 31-32:

The Examiner requests a more detailed explanation to what part "around a part" refers to. Applicants have amended the specification to clarify that the lid may fit snugly around a part of the microfluidic device.

4. Page 2, lines 1-3:

The Examiner requests a more detailed explanation of the term "injurious" as to what and why "injurious events" occur with open ports of a microfluidic device. Applicants have amended the application to clarify that it is "undesired events" that may occur due to open ports. Examples of undesired events can be found on page 1, lines 19-22 and lines 25-29.

5. Page 6, line 6:

The Examiner suggests inserting the word "there" between "which" and "are". Applicants have amended the specification in accord with the Examiner's kind suggestion.

6. Page 3, line 9:

The Examiner suggests inserting a space between "side" and "using". Applicants have amended the specification in accord with the Examiner's kind suggestion.

7. Page 3, lines 18-19:

The Examiner suggests a modification of the sentence for clarity. Applicants have amended the application in accord with the Examiner's kind suggestion.

8. Page 3, lines 24-27:

The Examiner asserts that the sentence is ambiguous. Applicants have amended the sentence for clarity.

9. Page 4, line 3:

The Examiner suggests inserting "m" after the Greek symbol to represent a micron. Applicants have amended the specification in accord with the Examiner's kind suggestion.

10. Page 4, line 17:

The Examiner suggests inserting a space between "may" and "be". Applicants have amended the specification in accord with the Examiner's kind suggestion.

11. Page 4, lines 28-30:

The Examiner alleges that the sentence is ambiguous. Applicants have amended the sentence for clarity.

12. Page 5, line 28:

The Examiner objects to the language "addition polymers" and requests a more detailed description. Applicants have amended the language to recite "additional polymers".

13. Page 5, line 30:

The Examiner suggests omitting "so" between "made" and "by". Applicants have amended the specification to clarify that the polymers can be "made to have low fluorescence by additives or bleaching".

14. Page 8, lines 4-6:

The Examiner objects to the language "avoiding trapping" as ambiguous. Applicants have amended the specification to clarify that the features of the subject structure allow for "avoiding the problem of trapping large volumes of air in the sealed area".

15. Page 8, lines 25-28:

The Examiner asserts that the sentence is unclear. Applicants have amended the specification to clarify that it is "all publications and patent applications mentioned in this specification" that are incorporated by reference.

IV. Objections to Claims

The Examiner objected to claim 12 for alleged informalities. Specifically, the Examiner alleges that "lead" should be "lid". Applicants have amended claim 12 according to the Examiner's kind suggestion.

V. Rejection under 35 C.F.R. §102

Claim 1 was rejected under 35 U.S.C. §102(b) as allegedly anticipated by Skold *et al.* (U.S. Patent No. 5,273,718). This rejection is respectfully traversed.

A. The Present Invention

The present invention solves the problem of evaporation with very small volumes and the problem of communication between individual units in a microfluidic device. The present invention describes a microfluidic device comprising a planar substrate with microstructures of channels and reservoirs formed therein. The openings to the microstructures have an aligned collar in relief formed at the upper opening of the microstructure. The microstructure wall may be aligned with the collar wall to have a smooth transition and be a single feature when the substrate is molded. Additionally, the collar inner wall may be offset from the inner wall of the microstructure serving as a fence around the microstructure. The device is sealed on the top by having a sealing cover lid or film contact the collar and form a seal with the collar upper surface. The lid may be of a conformable material or have an adhesive coating.

B. The Cited Art

SKOLD ET AL. describe an apparatus for carrying out biochemical reactions in microtiter plates. The apparatus of Skold *et al.* includes a gas pressure device comprising a substantially planar plate. The plate has an inflatable collar positioned on

the sides of the plate facing the microtiter plate. The collar may be inflated to contact the microtiter plate and form an air-tight seal between the gas pressure device and the microtiter plate.

C. Analysis

According to the M.P.E.P. § 2131, "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference".

Skold *et al.* fail to teach a microfluidic device with a planar substrate having at least one microstructure with an opening in the surface and at least a portion of the openings being surrounded by a collar in relief. The device of Skold *et al.* has a gas pressure device with a planar plate and an inflatable collar positioned on the sides of the plate. When the collar is inflated, a seal is formed between the gas pressure device and the microtiter plate. Nowhere does Skold *et al.* teach a planar substrate having at least one microstructure, much less a collar in relief positioned around the microstructure opening.

Accordingly, Applicants submit that standard of strict identity to maintain a rejection under 35 U.S.C. §102 has not been met. Withdrawal of the rejection under 35 U.S.C. §102(b) is respectfully requested.

VI. Rejections under 35 C.F.R. §103

Claims 2 and 6 were rejected under 35 U.S.C. §103 as allegedly obvious over Skold *et al.*

Claims 3-5 and 7-14 were rejected under 35 U.S.C. §103 as allegedly obvious over Skold *et al.* further in view of Dubrow *et al.* (U.S. Patent No. 6,251,343).

These rejections are respectfully traversed.

A. The Present Invention

The present invention is described above.

B. The Cited Art

SKOLD ET AL. is described above.

DUBROW ET AL. describe a microfluidic device comprising a body structure and a cover layer. The body structure has a planar, layered structure. The lower layer has at least one microscale channel network. The upper layer includes a plurality of ports in fluid communication with the channels of the lower layer. The cover layer has a plurality of apertures and mates with the body structure wherein the cover layer apertures are aligned with the plurality of ports of the body structure. Dubrow *et al.* attempts to solve the problem of introducing fluid volumes separately into different ports where the ports are small and close together, the problem of electrically isolating wells, as well as the problem of preventing spill-over from one well to another by providing a ridge surrounding the apertures of the cover layer.

C. Analysis

1. Legal Standard

According to the MPEP § 2143, "to establish a prima facie case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Third, the prior art references (or references when combined) must teach or suggest all the claim limitations."

2. Rejection over Skold et al.

As noted above, Skold *et al.* fail to show or suggest a planar substrate having at least one microstructure, much less a collar in relief positioned around the microstructure opening. The collar of Skold *et al.* is an inflatable collar on the planar surface of the gas pressure device. Further, Skold *et al.* fail to teach covering the collar with a lid of a conformable material or with an adhesive coating.

3. Rejection over Skold et al. in view of Dubrow et al.

As noted above, Skold *et al.* fail to show or suggest a planar substrate having at least one microstructure and a collar in relief positioned around the microstructure opening or covering the collar with a lid of a conformable material or a lid with an adhesive coating.

The teachings in Dubrow *et al.* when combined with Skold *et al.* do not make up for these deficiencies. Dubrow *et al.* is not concerned with sealing of a microfluidic device. The device of Dubrow *et al.* has a body structure and a cover layer that has a plurality of apertures and mates with the body structure. Dubrow *et al.* teach a ridge surrounding the apertures of the cover layer to prevent spill-over as well as to isolate the apertures electrically and spatially. Nowhere does Dubrow *et al.* teach sealing the microfluidic device.

In view of the above, Applicants respectfully request withdrawal of the rejections under 35 U.S.C. §103.

CONCLUSION

In view of the foregoing, Applicants submit that the claims pending in the application complies with the requirements of 35 U.S.C. §112 and patentably defines over the cited art. A Notice of Allowance is therefore respectfully requested.

The Examiner is invited to contact Applicants' representative at (650) 838-4410 if it is believed that prosecution of this application may be assisted thereby.

Respectfully submitted,

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Date: July 30, 2002

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the specification:

On page 1, please replace the paragraph starting on line 5 with the following:

This application claims the benefit of the filing date of U.S. provisional application [09/545,064]60/161,203 filed October 22, 2000, which disclosure is hereby incorporated by reference.

On page 1, please replace the paragraph starting on line 15 with the following:

Microfluidic devices offer great promise for the accurate manipulation of very small volumes, the rapid execution of a wide variety of operations, the minimal use of reagents, as well as many other benefits. As with all situations, the benefits come with challenges. For many purposes, one wishes to have a number of independent electrokinetic units in a single substrate. Since each unit will frequently comprise a plurality of reservoirs and channels, it is important that the individual units do not communicate except as required by the design of the device. Also important[ly,]to consider is the problem of evaporation with the very small volumes[, which]that are frequently involved with the operations[, due to evaporation]. Where there is an interest in doing a quantitative analysis of an operation involving kinetics, it is important that the solvent volume remain substantially constant, so that the concentrations of the reactants are not changing due to decreasing volume. To this end, methods are required to minimize evaporation. Additionally, particularly where long incubation times and/or long reaction times are involved, there is an interest in preventing contamination. A further concern is [adventitious]unintentional pressurization, during closing of a microstructure vessel, which could prematurely move the liquid from a reservoir into a channel.

On page 1, please replace the paragraph starting on line 30 with the following:

In response to these concerns, lids have been used to seal the ports of microfluidic devices. Lids may provide sealing through the pressure of their weight, by providing

adhesion, using various forms of latches or clasps, or by fitting snugly around a part of the microfluidic device and held by friction.

On page 2, please replace the paragraph starting on line 1 with the following:

There is an interest in developing devices and methods to substantially diminish the [injurious] undesired events that may occur due to open ports of a microfluidic device, where the devices are effective and can be readily fabricated and methods readily performed.

On page 2, please replace the paragraph starting on line 6 with the following:

U.S. Patent no. 5,[4]443,890 and references cited therein describe leakage-proof sealing of microfluidic devices. WO 99/43432 describes microfluidic devices and systems incorporating cover layers. U.S. Patent no. 5,545,280 describes applying adhesive to protrusions on a substrate.

On page 2, please replace the paragraph starting on line 26 with the following:

Fig. 1 is a plan view of a device with collars around microstructures; Fig. 1a is a cross-sectional view of the device of Fig. 1 along the partial phantom line[s] 1a-1a;

Fig. 2 is a plan view of the device of Fig. 1, with the collars removed to provide details of the individual units; Fig. 2a is a diagrammatic exploded view of the units of Fig. 2;

Fig. 3 is a side elevation cross-sectional view of a reservoir microstructure of a unit with a cover.

On page 3, please replace the paragraph starting on line 4 with the following:

The following examples are offered by way of illustration of the present invention, not limitation. Microfluidic devices are provided for manipulation of small volumes, where the devices comprise a substrate, usually an organic substrate in which there are channels and reservoirs, where the reservoirs have a raised collar above the planar surface of the substrate. A bottom film, including a rigid substrate, is adhered to and encloses the channels and the bottoms of the reservoirs. The reservoirs can be sealed on the top side using a film, which seals to the upper surface of the collar.

On page 3, please replace the paragraph starting on line 18 with the following:

The sealing cover or lid will be a film, which forms a seal about the collar[,so as] to at least substantially inhibit fluid flow from the reservoir. The cover will provide for sealing interaction with the collar upper surface, as a result of a compliant surface contacting the collar or an adhesive surface adhering to the upper surface of the collar, particularly an adhesive surface, which is removable. Contact will usually be minimal or not at all between the sealing cover or lid and the planar surface. The forces providing the sealing may be gravity, adhesive forces, or mechanical forces. For compliant surfaces, such as elastomeric films, skin-surface (closed-cell) foams, soft films, pressure would be applied[,]. The pressure may be [as] a result of a weighted backing, or a latching or gripping device[s] for holding the film against the collars[,]. The pressure may further be a result of a vacuum chuck which holds the film in position and can release the film, as appropriate, etc. The film may be stretched across the collars, held in position by clasps at he periphery of the substrate, a sealing pliable band around the periphery, a vacuum chuck, etc. A continuous sealing film may be used, which may be unrolled from a reel as the devices are moved in a continuous manner, for example, on a wheel or moving belt. The films may be natural rubber, polyisoprene, ethylene-propylene elastomers, polyurethane foams, polydimethylsiloxane, etc. The films may be thin or thick, so long as they have a minimum dimension, which provides for their sealing of the collars. Generally, the films will be at least about 50µm in thickness. Alternatively, films may be used, which have a thin adherent layer, which will adhere to the surface of the collar and after the film has fulfilled its function, the adhesive may be removed. Useful adhesives include pressure sensitive adhesives, such as ethylene-containing polymers, urethane polymers, butyl rubber, butadiene-acrylonitrile polymers, butadiene-acrylonitrile-isoprene polymers, and the like. See, for example, U.S. Patent no. 5,908,695 and references cited therein.

On page 4, please replace the paragraph starting on line 9 with the following:

The substrate will generally have a thickness of at least about 20µm, more usually at least about 40µm, and not more than about 0.5cm, usually not more than about 0.25cm. The width of the substrate will be determined by the number of units to be accommodated

and may be as small as about 2mm and up to about 6cm or more. The dimension in the other direction will generally be at least about 0.5cm and not more than about 20cm, usually not more than about 10cm. The substrate may be a flexible film or relatively inflexible solid, where the microstructures, such as reservoirs and channels, may be provided by embossing, molding, machining, etc. The collars may be formed at the same time using the same process, although more expensive processes may be used, such as photolithography or laser ablation. In this case, the collar regions would be protected while the substrate was eroded. The channel dimensions will generally be in the range of about 0.1μm to 1mm deep and about 0.5μm to 500μm wide, where the cross-section will generally be $0.1\mu m^2$ to about $0.25mm^2$. The channel lengths will vary widely depending on the operation for which the channel is to be used, generally being in the range of about 20nl to 1μl. The reservoirs may be cylindrically shaped or conically shaped, particularly inverted cones, where the diameter of the port will be from about 1.5 to 25 times, usually 1.5 to 15 times, the diameter of the bottom of the reservoir, where the reservoir connects to the channel.

On page 4, please replace the paragraph starting on line 28 with the following:

[Depending upon whether a film is embossed to produce the device or the device is molded, whether] Whether the microfeatures are left open will depend upon (i) whether a supporting film and/or an enclosing film is provided and/or (ii) whether the device is produced by embossing a film or by molding. The supporting film will generally be at least about 40μm and not more than about 5mm thick. The film used to enclose the channels and the bottom of the reservoirs will generally have a thickness in the range of about 10μm to 2mm, more usually in the range of about 20μm to 1mm. The selected thickness is primarily one of convenience and assurance of good sealing and the manner in which the devices will be used to accommodate instrumentation. Therefore, the ranges are not critical.

On page 5, please replace the paragraph starting on line 20 with the following:

As indicated, the substrate may be a flexible film or inflexible solid, so the method of fabrication will vary with the nature of the substrate. For embossing, at least two films will

be used, where the films may be drawn from rolls, one film embossed ant the other film adhered to the embossed film to provide a physical support. The individual units may be scored, so as to be capable of being used separately, or the roll of devices retained intact. See, for example, application serial no. PCT/98/21869. Where the devices are fabricated individually, they will usually be molded, using conventional molding techniques. The substrates and accompanying film will generally be plastic, particularly organic polymers, where the polymers include additional polymers, such as polyethers, polyesters, polyamides, polyimides, etc. Desirably, the polymers will have low fluorescence inherently or can be made [so]to have low fluorescence by additives or bleaching. The underlying enclosing film will then be adhered to a substrate by any convenient means, such as thermal bonding , adhesives, etc. The literature has many examples of adhering such films, see, for example, U.S. Patent nos. 4,558,333; and 5,500,071.

On page 7, please replace the paragraph starting on line 28 with the following:

The subject invention provides many advantages in enclosing, usually reversibly, small reservoirs or other microstructure. The subject collar structure has a small contact area, which serves to concentrate the force produced by whatever means of application of the lid onto a much smaller area, as compared to a cover which bonds to the entire surface of the device. A reduction in differential pressures created during application of the lid is achieved. Where the upper surface is flat, without areas in relief, a conformal lid comes down in such a way that it will usually first make contact with a large ring around the area to be sealed. The air trapped within this ring is pressurized into the volume to be sealed. By contrast, with the subject structure[,] the lid makes contact before it reaches the device main surface, and thereby avoiding the problem of trapping large volumes of air in the sealed area. In addition, for lid attachment mechanisms like gravity, friction and mechanical clips, where the force is not directly related to the contact area, the subject method increases the local pressure with which the lid is attached to the part. This increased pressure generally improves the seal and improves the proximity of conformal lids. This improved seal can enable the use of a weighted lid to produce an airtight seal without requiring a large mass or an extremely conformable lid material. Where the seal is substantially air tight, the lid will act to resist or prevent fluid flow. Capillary stop junctions

may be prone to failure by condensation or other mechanism, in which case the sealed lid provides a backup mechanism. Also, the sealed lid can easily counteract relatively strong fluidic forces, such as surface tension. Yet another advantage of the collar is that the effective leakage path (surface path) between two adjacent wells is increased. This increases the resistance to arcing due to high differential voltages in two adjacent wells. In fact, multiple concentric collars would be beneficial in further reducing this problem. Finally, during application and removal of a lid, there is a potential for liquids to wick between the lid and the surface of the device and microstructures. The short distance between the device and the lid can result in very strong capillary pressures. In the subject invention the lid is only in close proximity to the collar surface, so that fluid can only wick along that surface. By avoiding continuous ridges between different microstructures, movement of liquid between the microstructures can be obviated.

On page 8, please replace the paragraph starting on line 24 with the following:

All publications and patent applications mentioned in this specification are indicative of the level of skill of those skilled in the art to which this invention pertains. All publications and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication or patent application was specifically and individually indicated to be incorporated by reference.

In the claims:

2. (Amended) A microfluidic device according to Claim [1]3, wherein said collar has its inner surface aligned with the inner surface of said opening and a thickness of from about 0.05 to 0.5 mm thick extending away from said inner surface.

3. (Amended) A microfluidic device [according to Claim 2]comprising:

a substrate having a planar surface having at least one microstructure formed thereon, a plurality of openings in said surface of microstructures and at least a portion of said openings surrounded by a collar in relief, and wherein said collar is covered with a lid of a conformable material.

4. (Amended) A microfluidic device [according to Claim 2,]comprising:

a substrate having a planar surface having at least one microstructure formed thereon, a plurality of openings in said surface of microstructures and at least a portion of said openings surrounded by a collar in relief, and wherein said collar is covered with a lid with an adhesive coating.

5. (Amended) A microfluidic device according to Claim [1]3 produced by plastic molding.

12. (Amended) In a method employing a microfluidic device comprising introducing small volumes into microstructures, where the volumes comprise volatile solvents, the improvement which comprises: introducing said small volumes into a device according to Claims [1]3 or 4; and applying a compliant or adhesive [lead]lid to each of said collars.